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ORIGINAL RESEARCH

Impact of Obesity on Mortality in Hospitalized Patients with Pneumonia Due to 2009 H1N1 Influenza A Virus Versus Other Etiologies

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Abstract

Background: Reports from the 2009 H1N1 influenza A virus (2009 H1N1) pandemic indicate increased mortality in obese patients hospitalized with pneumonia. However, articles published prior to the pandemic have suggested that obesity may be a protective factor for mortality in these patients. The objective of this study was to compare the impact of obesity on mortality in hospitalized patients with pneumonia due to the 2009 H1N1 versus pneumonia due to other etiologies.

Methods: This was a secondary analysis of the CAPO international cohort study. Study groups were defined as follows: Group One, pneumonia due to 2009 H1N1: Patients hospitalized with pneumonia after March 2009 with a positive RT-PCR for 2009 H1N1 and Group Two, pneumonia due to other etiologies: Patients hospitalized with pneumonia before March 2009. Body Mass Index (BMI) was used to predict the influence of obesity on mortality. The effect of BMI on mortality was analyzed using a propensity-adjusted logistic regression model.

Results: From the total of 897 patients, 215 (24%) had pneumonia due to 2009 H1N1. After adjustment, increased BMI was associated with increased mortality in patients with pneumonia due to 2009 H1N1 and with decreased mortality in patients with pneumonia due to other etiologies.

Conclusions: Obesity is associated with poor outcomes in patients with pneumonia due to 2009 H1N1 but is protective in patients with pneumonia due to other etiologies. Defining the molecular mechanisms by which obesity influences outcomes in patients with pneumonia may help to develop novel therapeutic strategies.

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1 Introduction

Obesity is a growing pandemic. In the USA, 33% of adults are overweight, 34% are obese, and six percent are extremely obese.[1] In the general population, obesity is clearly associated with increased morbidity and mortality.[2,3] However, in the acutely ill hospitalized patient, controversy exists regarding the impact of obesity on patient mortality. Recent reports of acutely ill hospitalized patients with pneumonia due to 2009 H1N1 influenza A virus (2009 H1N1) suggested that increased BMI was associated with poor outcomes.[4–6] Obese patients with pneumonia due to 2009 H1N1 were more likely to require ICU care due to severe pneumonia with respiratory failure and acute respiratory distress syndrome (ARDS).[7] On the other hand, a meta-analysis published in 2009 indicated that hospitalized, acutely ill, obese patients were protected from poor outcomes.[8] This meta-analysis included a total of 88,051 obese and non-obese patients from 22 studies. Mortality of obese patients was statistically lower than in patients who were not obese. Several of these studies included patients with pneumonia. Since all of the analyzed studies predated the emergence of the 2009 H1N1 pandemic, we can conclude that patients with pneumonia included in these studies were infected with pathogens other than the 2009 H1N1 influenza A virus. A more recent publication reported decreased mortality in obese hospitalized patients with pneumonia due to *Streptococcus pneumonia* and *Haemophilus influenza*.[9]

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Table 1 Characteristics of hospitalized patients with pneumonia enrolled in the CAPO international cohort study by etiology of pneumonia

Variable	Pneumonia due to 2009 H1N1 n=215 n (%)	Pneumonia due to Other Etiologies n=682 n (%)	P-value
Age ≥65	26 (12.1)	372 (54.5)	<0.001
Age, Mean (SD)	43.9 (17.4)	65.2 (16.8)	<0.001
Male Gender	97 (45.1)	551 (80.8)	<0.001
BMI, Mean (SD)	27.8 (7.7)	25.9 (5.2)	<0.001
BMI Class			
>30.0 kg/m^2 (Obese)	62 (28.8)	152 (22.3)	
25.0-29.9 kg/m^2 (Overweight)	42 (19.5)	170 (24.9)	0.082
18.5-24.9 kg/m^2 (Normal Weight)	111 (51.6)	260 (52.8)	
Nursing Home Resident	2 (0.9)	36 (5.7)	0.004
Diabetes	30 (14.1)	170 (26.6)	0.002
COPD	27 (12.6)	256 (37.5)	<0.001
HIV Disease	1 (0.5)	100 (14.7)	<0.001
Congestive Heart Failure	17 (8)	140 (22.2)	<0.001
Liver Disease	5 (2.3)	46 (7.2)	0.009
Neoplastic Disease	6 (2.8)	77 (12.2)	<0.001
Renal Disease	11 (5.2)	89 (14)	0.001
Cerebrovascular Accident	2 (0.9)	83 (13.2)	<0.001
Albumin ≤3.5 g/dl	50 (59.5)	120 (80.5)	<0.001
Blood urea nitrogen ≥30 mg/dl	67 (33.3)	165 (28.1)	0.157
Sodium <130 mmol/L	23 (10.7)	78 (11.4)	0.765
PaO_2 <60 mm Hg	142 (66)	323 (47.4)	<0.001
Temperature <95°C or >104°C	3 (1.4)	24 (3.5)	0.112
Heart Rate ≥125 Beats/Min	30 (14.1)	78 (11.5)	0.304
Respiratory Rate >30 Breaths/Min	59 (27.7)	72 (10.8)	<0.001
Systolic Blood Pressure <90 mm Hg	10 (4.7)	38 (5.6)	0.601
Altered Mental Status	29 (13.5)	90 (13.2)	0.912
ICU Admission	67 (31.6)	89 (14)	<0.001
PSI Risk Class IV or V	43 (20)	359 (52.6)	<0.001
CURB-65 Score II, III or IV	84 (39.1)	146 (21.5)	<0.001

Based on the current literature, it can be hypothesized that the impact of obesity on the clinical outcomes of hospitalized patients with pneumonia may be different based on the etiologic agent. Obese patients with pneumonia due to 2009 H1N1 may be at high risk for mortality, whereas obese patients with pneumonia due to other etiologies may be at a lower risk for mortality. The aim of the present study was to compare the effect of obesity on the mortality of hospitalized patients with pneumonia due to 2009 H1N1 versus patients with pneumonia due to other etiologies.

2 Materials & Methods

2.1 Study Design and Patients

This was a secondary data analysis of patients with pneumonia enrolled in the Community-Acquired Pneumonia Organization (CAPO) International Cohort Study.[10] Data collection for the CAPO study started in April 2000. The study is currently enrolling patients hospitalized with pneumonia from 55 centers in 20 countries. Copies of the study protocol and data collection form are available at the study website.[11] Institutional review board approval was obtained from all participating institutions.

2.2 Inclusion criteria

1. Patients hospitalized with pneumonia fulfilling the following criteria: Presence of a new pulmonary infiltrate on chest radiograph at the time of hospital admission and either a new or increased cough with or without sputum production, an abnormal temperature (< 35.6°C or > 37.8°C), or an abnormal serum leukocyte count (e.g., leukocytosis, left shift, or leukopenia).[12]

2. Patients with available data to calculate body mass index (BMI).

2.3 Study Groups

Patients were classified into two groups:

- *Group A, Pneumonia due to 2009 H1N1:* Patients hospitalized with pneumonia after May 2009 with an RT-PCR test positive for 2009 H1N1 influenza A virus.

- *Group B, Pneumonia due to other etiologies:* Patients hospitalized with pneumonia before May 2009.

2.4 Predictor Variable

The predictor variable was Body Mass Index (BMI), defined as the weight in kilograms divided by the square of the height in meters (kg/m^2).

2.5 Outcome Variable

The outcome variable was mortality for any cause during the hospitalization.

2.6 Confounding variables

A total of 24 confounding variables were collected including patient demographics, comorbidities and laboratory characteristics.

2.7 Statistical analysis

Baseline patient characteristics between those with pneumonia due to 2009 H1N1 versus those with pneumonia due to other etiologies were compared using the chi-squared or Fisher's Exact tests for categorical variables and the Mann-Whitney U-test for continuous variables. To examine the adjusted effect of the etiology of pneumonia on patient mortality for a given BMI, a propensity-adjusted logistic regression model was used. The

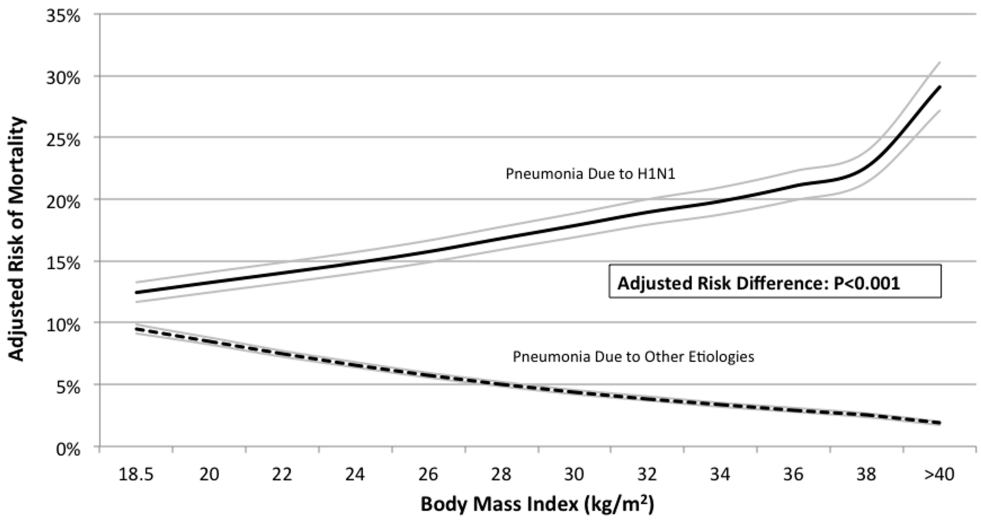

Fig. 1 Propensity-adjusted risk of mortality by body mass index for hospitalized patients in the CAPO international cohort with pneumonia due to H1N1 compared to hospitalized patients with pneumonia due to other etiologies.

propensity score adjustment methodology allows for the condensing of multiple confounding variables into one score. This may reduce error from including too many confounding variables in a multivariate regression model when the outcome of interest in the study population is infrequent. Although initially developed for models examining treatment effects, this methodology has shown validity for controlling for confounding when examining non-treatment predictor variables.[13] All of the variables listed in **Table 1** with *P*-values of $\leq$0.15 were used to create the propensity score. Since BMI was the outcome of the creation of the propensity score, it was not included as an independent variable in its creation. As it was not expected that the propensity score predicted mortality linearly, the score was partitioned into five equal sized categories.[14] A logistic regression model was then created to determine the propensity-adjusted risk of mortality for a given BMI. The final model included the following variables: BMI, pneumonia etiology (2009 H1N1 versus other etiologies), an interaction term between the etiology of pneumonia and BMI, and the five levels of the categorized propensity score. The interaction term was included in the model to determine if the propensity-adjusted risk of mortality was statistically different for each etiology of pneumonia. P-values of $\leq$0.05 were considered statistically significant. SAS v9.2 (SAS Inc., Cary, NC) and MedCalc v11 (Mariakerke, Belgium) were used for all analyses.

3 Results

3.1 Study Patients

A total of 897 patients were included in the study. Mean age of all patients was 60 years (SD=19), and 648 patients were male (72%). According to BMI, 53% of patients were within the normal BMI range, 24% of patients were overweight (BMI: 25-29.9 kg/m^2); and 24% of patients were obese (BMI>30 kg/m^2). Of the obese patients, 61% had a BMI between 30-35 kg/m^2; 18% had a BMI between 35-40 kg/m^2; and 21% had a BMI > 40 kg/m^2.

A total of 215 (24%) patients had a confirmed diagnosis of 2009 H1N1 influenza A virus. Characteristics of the study population according to the etiology of pneumonia are included in **Table 1**.

All of the patients received adequate antibiotic therapy according to national guidelines. Appropriate antiviral treatment was given to 191 of the patients with confirmed 2009 H1N1 influenza A virus infection (189 with oseltamivir and 2 with zanamivir). A total of 60 of these patients (29%) were treated with steroids.

3.2 Study Outcomes

A total of 36 (42%) patients with pneumonia due to 2009 H1N1 died, compared with 179 (22%) patients with pneumonia due to other etiologies (P<0.001). The propensity-adjusted risk curves indicating the predicted risk of mortality in relation to the BMI for each study arm are shown in **Figure 1**. The adjusted risk of mortality increased with increased BMI for patients with pneumonia due 2009 H1N1. Contrary to this, the adjusted risk of mortality decreased with increased BMI for patients with pneumonia due to other etiologies. There was a statistically significant difference between the risks of mortality by BMI for the two study groups (P<0.001).

4 Discussion

This study indicates that the impact of obesity on the mortality of hospitalized patients with pneumonia is influenced by the etiologic agent. In patients with pneumonia due to 2009 H1N1, obesity is associated with increased mortality. On the other hand, in patients with pneumonia due to other etiologies, obesity has a protective effect on mortality.

Several investigators have reported an association of obesity with poor outcomes in patients with pneumonia infected with 2009 H1N1.[4–7] Animal studies indicate that the production of interferon is significantly decreased in diet-induced, obese mice when compared to lean, control animals.[15,16] Decreased production of

interferon in obese patients may explain the poor outcomes associated with pneumonia due to 2009 H1N1 influenza A virus.

The role of obesity in the outcomes of pneumonia patients infected with pathogens other than 2009 H1N1 influenza A virus have been reported in three prior publications. First, a longitudinal study of pneumonia hospitalizations and mortality including 5,677 men and women 55 years of age and older found that, after adjusting for chronic conditions, the risk of pneumonia death was lower in those with the highest BMI.[17] Second, a study of 110,792 patients found that a high BMI ($\geq$25Kg/m^2) was protective for pneumonia-related mortality in middle-aged and elderly community residents.[18] Third, a recent study from a single center indicated a decreased risk of pneumonia death in patients with higher BMI infected with *Streptococcus pneumoniae* or *Haemophilus influenzae*.[19] Our findings are in agreement with these three studies indicating that obesity is a protective factor for mortality in patients with pneumonia who are not infected with 2009 H1N1 influenza A virus. It is unclear why obese patients may be protected from poor outcomes when pneumonia is due to a bacterial pathogen.

Obese patients have a low-grade chronic inflammatory state produced by both classic cytokines and adipose tissue released adipocytokines such as leptin or adiponectine.[20,21] This abnormal inflammatory state is known to be detrimental to several organ systems, and may accelerate the progression of chronic diseases such as atherosclerosis and diabetes. It can be speculated that the abnormal cytokine milieu present in obese patients may be protecting against the systemic inflammatory response that characterizes severe bacterial pneumonia.

Our study has several limitations. Although there are more than 7,000 patients in the CAPO database, data on BMI was available in only 17% of these cases. Lack of BMI in databases of patients with infections has been mentioned as an important limitation in the study of the role of obesity in patients with infections.[22] Timing of antiviral therapy has been considered an important determinant of outcomes in patients with pneumonia due to 2009 H1N1.[23] In our database, the timing of initiation of symptoms prior to admission to the hospital was not available in a significant number of patients. Because of this, timing of initiation of symptoms to initiation of antiviral therapy was not available. Finally, several variables that are not available in the database may confound the relationship between obesity and mortality in our patients. This may bias the results.

Our data were strengthened by the following factors: First, the data represents patients from multiple countries, thereby increasing generalizability. Second, we used RT-PCR for confirmatory diagnosis of 2009 H1N1. By excluding patients enrolled in the CAPO database after the start of the 2009 H1N1 pandemic, we can reasonably assume that no patient in the control group was infected with this virus.

In conclusion, this study indicates that obesity is an independent prognostic factor for mortality in patients with pneumonia. Elevated BMI is associated with a significant increase in mortality in hospitalized patients with pneumonia due to 2009 H1N1 influenza A virus. On the other hand, an elevated BMI is a protective factor for mortality in hospitalized patients with pneumonia due to etiologies other than 2009 H1N1 influenza. The pathogenesis underlying this opposite effect of obesity on mortality in relation with the etiology of pneumonia is unknown. Understanding the causes that place an obese host with pneumonia at increased or decreased risk for mortality according to the etiology of pulmonary infection may help to develop new treatment strategies for obese patients with acute infections.

Conflicts of Interest: JAR has received research support from and is a consultant for Pfizer. He is also has received lecture honoraria from Merck, Pfizer and Wyeth Pharmaceuticals. RTH, MAEG, TLW, PP and CBJ have no conflicts to report.

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References

1 C. for Disease Control, Prevention *et al.*, "Prevalence of overweight, obesity and extreme obesity among adults: United states, trends 1960-62 through 2005-2006," *National Center for Health statistics*, 2009. [Online]. Available: <http://www.cdc.gov/nchs/data/hestat/overweight/overweight_adult.htm> (updatedDecember23,2009September9,2010)

2 T. Byers, "Body weight and mortality," *New England Journal of Medicine*, vol. 333, no. 11, pp. 723–724, 1995.

3 I.-M. Lee, J. E. Manson, C. H. Hennekens, and R. S. Paffenbarger, "Body weight and mortality: a 27-year follow-up of middle-aged men," *Jama*, vol. 270, no. 23, pp. 2823–2828, 1993.

4 L. Vaillant, G. La Ruche, A. Tarantola, and P. Barboza, "Epidemiology of fatal cases associated with pandemic h1n1 influenza 2009." *Euro surveillance: bulletin europeen sur les maladies transmissibles= European communicable disease bulletin*, vol. 14, no. 33, pp. 127–136, 2008.

5 A. Kumar, R. Zarychanski, R. Pinto, D. J. Cook, J. Marshall, J. Lacroix, T. Stelfox, S. Bagshaw, K. Choong, F. Lamontagne *et al.*, "Critically ill patients with 2009 influenza a (h1n1) infection in canada," *Jama*, vol. 302, no. 17, pp. 1872–1879, 2009.

6 O. W. Morgan, A. Bramley, A. Fowlkes, D. S. Freedman, T. H. Taylor, P. Gargiullo, B. Belay, S. Jain, C. Cox, L. Kamimoto *et al.*, "Morbid obesity as a risk factor for hospitalization and death due to 2009 pandemic influenza a (h1n1) disease," *PloS one*, vol. 5, no. 3, p. e9694, 2010.

7 C. for Disease Control, P. (CDC *et al.*, "Intensive-care patients with severe novel influenza a (h1n1) virus infection-michigan, june 2009." *MMWR. Morbidity and mortality weekly report*, vol. 58, no. 27, p. 749, 2009.

8 C. W. Hogue, J. D. Stearns, E. Colantuoni, K. A. Robinson, T. Stierer, N. Mitter, P. J. Pronovost, and D. M. Needham, "The impact of obesity on outcomes after critical illness: a

meta-analysis," *Intensive care medicine*, vol. 35, no. 7, p. 1152, 2009.

9 V. F. Corrales-Medina, J. Valayam, J. A. Serpa, A. M. Rueda, and D. M. Musher, "The obesity paradox in community-acquired bacterial pneumonia," *International Journal of Infectious Diseases*, vol. 15, no. 1, pp. e54–e57, 2011.

10 J. A. Ramirez, "Fostering international multicenter collaborative research: the capo project [research methods]," *The International Journal of Tuberculosis and Lung Disease*, vol. 11, no. 10, pp. 1062–1065, 2007.

11 "University of louisville division of infectious diseases. community-acquired pneumonia organization (capo)," Updated 2010. [Online]. Available: www.caposite.com

12 L. A. Mandell, R. G. Wunderink, A. Anzueto, J. G. Bartlett, G. D. Campbell, N. C. Dean, S. F. Dowell, T. M. File, D. M. Musher, M. S. Niederman *et al.*, "Infectious diseases society of america/american thoracic society consensus guidelines on the management of community-acquired pneumonia in adults," *Clinical infectious diseases*, vol. 44, no. Supplement 2, pp. S27–S72, 2007.

13 D. J. Pasta, "Using propensity scores to adjust for group differences: Examples comparing alternative surgical methods." Paper presented at: 25th Annual SAS Users Group International Conference; Indianapolis, IN, 2000.

14 J. Ramirez, S. Aliberti, M. Mirsaeidi, P. Peyrani, G. Filardo, A. Amir, B. Moffett, J. Gordon, F. Blasi, and J. Bordon, "Acute myocardial infarction in hospitalized patients with community-acquired pneumonia," *Clinical infectious diseases*, vol. 47, no. 2, pp. 182–187, 2008.

15 A. G. Smith, P. A. Sheridan, J. B. Harp, and M. A. Beck, "Diet-induced obese mice have increased mortality and altered immune responses when infected with influenza virus," *The Journal of nutrition*, vol. 137, no. 5, pp. 1236–1243, 2007.

16 A. G. Smith, P. A. Sheridan, R. J. Tseng, J. F. Sheridan, and M. A. Beck, "Selective impairment in dendritic cell function and altered antigen-specific cd8+ t-cell responses in diet-induced obese mice infected with influenza virus," *Immunology*, vol. 126, no. 2, pp. 268–279, 2009.

17 A. Z. LaCroix, S. Lipson, T. P. Miles, and L. White, "Prospective study of pneumonia hospitalizations and mortality of us older people: the role of chronic conditions, health behaviors, and nutritional status." *Public health reports*, vol. 104, no. 4, p. 350, 1989.

18 Y. Inoue, A. Koizumi, Y. Wada, H. Iso, Y. Watanabe, C. Date, A. Yamamoto, S. Kikuchi, Y. Inaba, H. Toyoshima *et al.*, "Risk and protective factors related to mortality from pneumonia among middleaged and elderly community residents: the jacc study," *Journal of epidemiology*, vol. 17, no. 6, pp. 194–202, 2007.

19 V. F. Corrales-Medina, J. Valayam, J. A. Serpa, A. M. Rueda, and D. M. Musher, "The obesity paradox in community-acquired bacterial pneumonia," *International Journal of Infectious Diseases*, vol. 15, no. 1, pp. e54–e57, 2011.

20 M. E. Falagas and M. Kompoti, "Obesity and infection," *The Lancet infectious diseases*, vol. 6, no. 7, pp. 438–446, 2006.

21 V. Vachharajani, "Influence of obesity on sepsis," *Pathophysiology*, vol. 15, no. 2, pp. 123–134, 2008.

22 R. Huttunen and J. Syrjänen, "Obesity and the outcome of infection," *The Lancet infectious diseases*, vol. 10, no. 7, pp. 442–443, 2010.

23 E. Bautista, T. Chotpitayasunondh, Z. Gao, S. Harper, M. Shaw, T. Uyeki, S. Zaki, F. Hayden, D. Hui, J. Kettner *et al.*, "Clinical aspects of pandemic 2009 influenza a (h1n1) virus infection." *The New England journal of medicine*, vol. 362, no. 18, pp. 1708–1719, 2010.